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Original article

Ribociclib plus letrozole in early breast cancer: A presurgical, window-of-opportunity study

G. Curigliano [a, *], P. Gómez Pardo [b], F. Meric-Bernstam [c], P. Conte [d, e], M.P. Lolkema [f, g], J.T. Beck [h], A. Bardia [i], M. Martínez García [j], F. Penault-Llorca [k], S. Dhuria [l], Z. Tang [l], N. Solovieff [m], M. Miller [l], E. Di Tomaso [m], S.A. Hurvitz [n]

[a] Istituto Europeo di Oncologia, via Ripamonti 435, 20141, Milan, Italy
[b] Servicio Oncologia Médica, Vall d'Hebron University Hospital, Vall d'Hebron 119–129, 08035, Barcelona, Spain
[c] The University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd, Houston, TX, 77030, USA
[d] Istituto Oncologico Veneto, Via Gattamelata 64, 35128, Padua, Italy
[e] University of Padova, Via Giustiniani 22, 35121, Padua, Italy
[f] University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands
[g] Erasmus Medical Center Cancer Institute, Erasmus Medical Center, s-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands
[h] Highlands Oncology Group, 3232 N North Hills Blvd, Fayetteville, AR, 72703, USA
[i] Massachusetts General Hospital Cancer Center, Harvard Medical School, 55 Fruit Street, Boston, MA, 02114, USA
[j] Oncología Médica, Hospital del Mar, Passeig Marítim 25-29, 08003, Barcelona, Spain
[k] Centre Jean Perrin, Unicancer and EA 4677 Université d'Auvergne, 58 rue Montalembert, 63011, Clermont-Ferrand, France
[l] Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ, 07936-1080, USA
[m] Novartis Institutes for BioMedical Research, 230 Massachusetts Avenue, Cambridge, MA, 02139, USA
[n] University of California, Los Angeles, 2825 Santa Monica Blvd, Suite 211, Santa Monica, CA, 90404, USA

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ABSTRACT

Objectives: Cyclin D–cyclin-dependent kinase (CDK) 4/6–inhibitor of CDK4/6–retinoblastoma (Rb) pathway hyperactivation is associated with hormone receptor-positive (HR+) breast cancer (BC). This study assessed the biological activity of ribociclib (LEE011; CDK4/6 inhibitor) plus letrozole compared with single-agent letrozole in the presurgical setting.

Materials and methods: Postmenopausal women ($N = 14$) with resectable, HR+, human epidermal growth factor receptor 2-negative (HER2−) early BC were randomized 1:1:1 to receive 2.5 mg/day letrozole alone (Arm 1), or with 400 or 600 mg/day ribociclib (Arm 2 or 3). Circulating tumor DNA and tumor biopsies were collected at baseline and, following 14 days of treatment, prior to or during surgery. The primary objective was to assess antiproliferative response per Ki67 levels in Arms 2 and 3 compared with Arm 1. Additional assessments included safety, pharmacokinetics, and genetic profiling.

Results: Mean decreases in the Ki67-positive cell fraction from baseline were: Arm 1 69% (range 38–100%; $n = 2$), Arm 2 96% (range 78–100%; $n = 6$), Arm 3 92% (range 75–100%; $n = 3$). Decreased phosphorylated Rb levels and *CDK4*, *CDK6*, *CCND2*, *CCND3*, and *CCNE1* gene expression were observed following ribociclib treatment. Ribociclib and letrozole pharmacokinetic parameters were consistent with single-agent data. The ribociclib plus letrozole combination was well tolerated, with no Grade 3/4 adverse events over the treatment.

Conclusion: The results suggest absence of a drug–drug interaction between ribociclib and letrozole and indicate ribociclib plus letrozole may reduce Ki67 expression in HR+, HER2− BC (NCT01919229).

Introduction

Endocrine therapy is a key treatment strategy for hormone receptor-positive (HR+) breast cancer due to the dependency of these tumors on estrogen signaling [1]. Combining endocrine

* Corresponding author. Tel.: +39 02 57489439; fax: +39 02 94379224.
E-mail address: giuseppe.curigliano@ieo.it (G. Curigliano).

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therapy with targeted therapies may enhance the effect of treatment by targeting compensatory pathways that act downstream of estrogen signaling. Short-term, window-of-opportunity studies of drug combinations can inform the optimal biological dose [2], enable the investigation of pharmacodynamic (PD) markers, identify biomarkers for patient selection, and may expedite drug development [3]. Moreover, short-term endpoints in window-of-opportunity studies, such as cell proliferation as measured by Ki67, can act as surrogate markers of longer-term patient outcomes [4], and several short-term studies have contributed to treatment decisions for endocrine therapy, including the potential of combination therapies [5] and the preferred patient biomarker profile [6].

The cyclin D–cyclin-dependent kinase (CDK) 4/6–inhibitor of CDK4/6 (INK4)–retinoblastoma (Rb) pathway acts downstream of estrogen receptor (ER) activation to promote cell cycle progression and cell division in response to estrogen signaling [7]. As such, endocrine therapy inhibits activation of this pathway, down-regulating cell proliferation [8]. Recent data demonstrate that endocrine therapy-resistant tumor cells are able to maintain cyclin D–CDK4/6–INK4–Rb pathway activity [1]. Additionally, the cyclin D–CDK4/6–INK4–Rb pathway is frequently disrupted in favor of cell cycle progression in HR+ breast cancer [9–11] and has been associated with poor clinical outcome [1]. Therefore, targeting the cyclin D–CDK4/6–INK4–Rb pathway may present an effective strategy to enhance the efficacy of endocrine therapies.

Ribociclib (LEE011) is an orally bioavailable, selective inhibitor of CDK4/6 that prevents Rb phosphorylation, resulting in G1 cell cycle arrest *in vitro* [12,13]. Ribociclib has exhibited synergistic activity with letrozole in preclinical xenograft models of ER-positive (ER+) breast cancer [14]. In clinical trials, ribociclib has demonstrated clinical activity both as a single agent in patients with advanced solid tumors, and when administered in combination with letrozole to patients with advanced ER+, human epidermal growth factor receptor 2-negative (HER2−) breast cancer [15,16].

We report results of a Phase II, window-of-opportunity, pre-surgical treatment study evaluating the safety, pharmacokinetics (PK), and PD of two clinical doses of ribociclib (400 mg and 600 mg) in combination with letrozole versus single-agent letrozole in HR+ early breast cancer (ClinicalTrials.gov study number: NCT01919229).

Material and methods

Study design

The primary objective of this multicenter, randomized study (Fig. 1) was to assess the difference in antiproliferative activity of ribociclib in combination with letrozole versus single-agent letrozole, as measured by changes in expression level of the proliferative marker Ki67 from baseline to time of surgery. Secondary objectives included the assessment of safety, tolerability, and PK of ribociclib and letrozole in combination, and the evaluation of PD markers related to ribociclib activity in breast cancer. The study also evaluated potential correlations between ribociclib exposure and major safety and biomarker parameters, changes in biomarkers related to the cyclin D–CDK4/6–INK4–Rb pathway, and the role of circulating tumor DNA (ctDNA) as a potential platform for molecular characterization. Patients were treated with once-daily letrozole 2.5 mg (Arm 1), with or without once-daily ribociclib 400 mg (Arm 2) or 600 mg (Arm 3) for 14 days (±3 days) prior to surgery.

Patient population

Adult postmenopausal women with treatment-naïve, newly diagnosed, surgically resectable, Grade II/III HR+, HER2− invasive breast cancer were included in this study. Patients were required to have at least one breast lesion with a diameter of ≥1.0 cm confirmed by ultrasound, mammography, computed tomography, or magnetic resonance imaging. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate bone marrow and organ function. Patients were excluded based on the presence of a concurrent malignancy or a history of malignancy within 3 years of randomization, with the exception of adequately treated basal cell skin cancer, squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer. Key exclusion criteria also included active cardiac disease or a history of cardiac dysfunction, including having a left ventricular ejection fraction of <50% as determined by a multiple-gated acquisition scan or an echocardiogram, and a QT corrected using Fridericia's formula (QTcF) of >450 ms. Patients were excluded if they were receiving medications that are known strong inducers or inhibitors of cytochrome P450 3A4 (CYP3A4), have a narrow therapeutic window and are predominantly metabolized through CYP3A4, or have a known risk of prolonging the QT interval or inducing Torsades de Pointes.

Safety assessments

Safety assessments were conducted at baseline and at scheduled intervals throughout the study. Hematology, blood chemistry, thyroid function, vital signs, and physical condition were regularly monitored. Cardiac function was monitored by performing triplicate electrocardiograms (ECGs) within 72 h prior to randomization and again on Days 1, 8, and 14 at the following time points: pre-dose and 2, 4, and 6 h after treatment dose. In each case, the ECG measurements were collected prior to PK sampling. In addition, patients were fitted with a Mortara H12+ Holter (Mortara Instrument, Milwaukee, WI, USA) instrument to carry out continuous ECG recordings over a 24-h period both at baseline (within 1 day prior to the first dose) and on Day 14 approximately 24 h prior to surgery. Adverse events (AEs) were assessed continuously according to the Common Terminology Criteria for Adverse Events version 4.03.

Pharmacokinetic assessments

Blood samples for the analysis of ribociclib and letrozole plasma concentrations were collected on Days 1, 8, and 14 at pre-dose and 2, 4, and 6 h after treatment dose. An additional PK blood sample was collected on Day 15 approximately 24 h after the last treatment dose on Day 14 and immediately prior to surgery. Plasma concentrations were measured using validated liquid chromatography–tandem mass spectrometry with a lower limit of quantification (LLOQ) of approximately 1.0 ng/mL for ribociclib and 2.0 ng/mL for letrozole. PK parameters were derived from individual plasma concentration–time profiles using non-compartmental analysis (Phoenix®; Pharsight, Mountain View, CA, USA) and were summarized using descriptive statistics.

Pharmacodynamic and biomarker assessments

Both tumor tissue samples and plasma samples for ctDNA were collected at baseline prior to the first dose of treatment and on Day 15 (±3 days) at, or immediately prior to, surgery. Blood samples for estradiol assessment were collected prior to the first dose of study treatment and prior to surgery on Day 14 (±3 days). Immunohistochemistry (IHC) detection of Ki67-positive tumor cells was performed on baseline and surgery tumor tissue samples to assess changes in the percentage of positive tumor cells. To assess the PD activity of ribociclib, changes in S780-phosphorylated Rb (pRb) levels in tumor samples were evaluated by IHC with H-score values

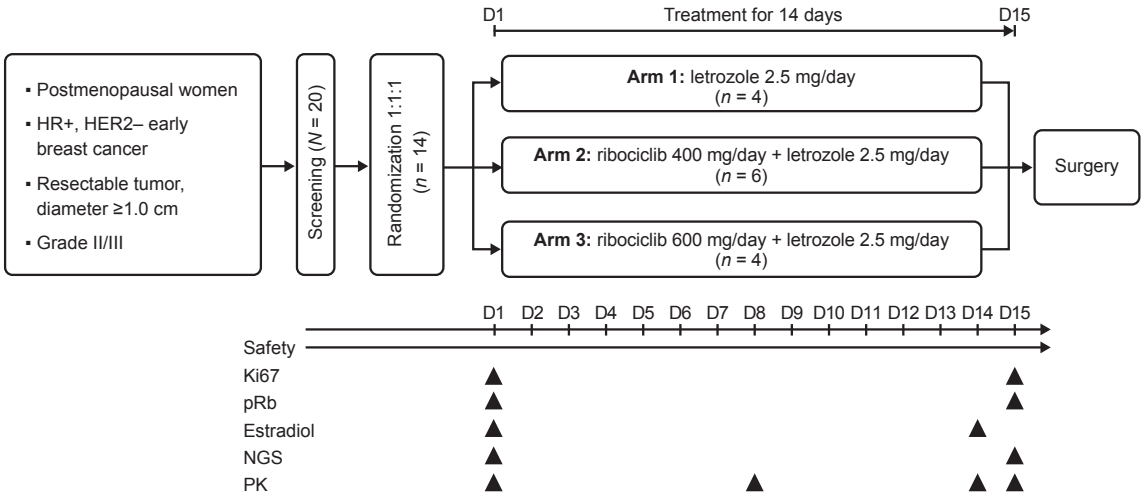


Fig. 1. Study design. **Abbreviations:** D: day; HER2−: human epidermal growth factor receptor 2-negative; HR+: hormone receptor-positive; NGS: next-generation sequencing; PK: pharmacokinetics; pRb: phosphorylated retinoblastoma. Tumor biopsy and blood samples were collected during treatment on the indicated days for the assessment of Ki67 expression, pRb level, and estradiol concentration, and for NGS and PK analysis.

calculated for each time point. To assess the PD activity of letrozole, estradiol serum concentrations were evaluated using an enzyme-linked immunosorbent assay. Paired tumor tissue samples were used to analyze the expression of genes involved in the cyclin D–CDK4/6–INK4–Rb pathway using NanoString® technology. Next-generation sequencing (NGS) of all ctDNA and tumor tissue samples was performed using a 542-gene targeted panel to assess potential molecular alterations in genes associated with ER+ breast cancer.

Results

Patient characteristics and disposition

Table 1 summarizes the characteristics of all patients enrolled in the study. From October 10, 2013 to July 17, 2014, 14 patients with a median age of 65 years (range 51–78 years) were randomized to one of three treatment arms: letrozole 2.5 mg/day (Arm 1, $n = 4$), letrozole 2.5 mg/day plus ribociclib 400 mg/day (Arm 2, $n = 6$) or 600 mg/day (Arm 3, $n = 4$). Thirteen patients (93%) completed treatment; one patient in Arm 3 discontinued due to patient decision. This study was prematurely terminated on July 17, 2014, due to low patient enrollment.

Safety and tolerability

All AEs suspected to be related to study treatment were mild or moderate in severity with no associated Grade 3/4 AEs. AEs of any grade suspected to be study drug-related occurred in 25% of patients in Arm 1 (1/4), 50% of patients in Arm 2 (3/6), and 100% of patients in Arm 3 (4/4). Two AEs suspected to be related to study treatment occurred in Arm 1: nausea and hypomagnesemia ($n = 1$ each; both Grade 1/2; Table 2). The most frequent treatment-related AEs ($n > 1$) in Arms 2 or 3 were nausea, asthenia, QTcF prolongation, and decreased appetite ($n = 2$ each; all Grade 1/2). One patient in Arm 3 experienced an asymptomatic increase in QTcF from baseline of >60 ms–490 ms. Six patients had QTcF changes of >30 ms (Arm 1, $n = 2$; Arm 2, $n = 1$; Arm 3, $n = 3$).

Pharmacokinetics

Following oral dosing, both ribociclib and letrozole were rapidly absorbed, with maximum plasma concentration (C_{max}) achieved between 2 and 4 h and 2 h, respectively, after both single (Day 1) and multiple (Day 8 and Day 14) doses (Table 3). The plasma concentration of ribociclib increased two- to three-fold from Day 1 to

Table 1
Patient characteristics.

Characteristic	Arm 1: Letrozole 2.5 mg/day ($n = 4$)	Arm 2: Ribociclib 400 mg/day + letrozole 2.5 mg/day ($n = 6$)	Arm 3: Ribociclib 600 mg/day + letrozole 2.5 mg/day ($n = 4$)	All patients ($N = 14$)
Age, years, median (range)	57 (51–63)	65 (51–78)	70 (66–75)	65 (51–78)
Age, n (%)				
<65 years	4 (100)	3 (50)	0	7 (50)
≥65 years	0	3 (50)	4 (100)	7 (50)
Race, n (%)				
Caucasian	4 (100)	6 (100)	4 (100)	14 (100)
Ethnicity, n (%)				
Hispanic	1 (25)	0	0	1 (7)
Not reported	3 (75)	0	0	3 (21)
Other	0	5 (83)	3 (75)	8 (57)
Unknown	0	1 (17)	1 (25)	2 (14)
BMI, kg/m^2, median (range)	28 (21–36)	29 (27–43)	26 (25–34)	29 (21–43)
ECOG PS, n (%)				
0	4 (100)	4 (67)	3 (75)	11 (79)
1	0	2 (33)	1 (25)	3 (21)

Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Table 2
All-grade adverse events suspected to be study treatment-related (≥15% in any treatment arm).

Adverse event, *n* (%)	Arm 1: Letrozole 2.5 mg/day ($n = 4$)	Arm 2: Ribociclib 400 mg/day + letrozole 2.5 mg/day ($n = 6$)	Arm 3: Ribociclib 600 mg/day + letrozole 2.5 mg/day ($n = 4$)
Total	1 (25)	3 (50)	4 (100)
Abdominal pain	0	0	1 (25)
Diarrhea	0	0	1 (25)
Nausea	1 (25)	0	2 (50)
Stomatitis	0	1 (17)	0
Vomiting	0	0	1 (25)
Asthenia	0	1 (17)	1 (25)
Fatigue	0	0	1 (25)
QTcF prolongation	0	0	2 (50)
Decreased appetite	0	0	2 (50)
Hypomagnesemia	1 (25)	0	0
Dyspnea	0	1 (17)	0
Hot flush	0	0	1 (25)

Day 14 for both doses, consistent with the described half-life of ≈30 h [17], with steady-state reached by approximately Day 8. Ribociclib exposure increased with increasing doses from 400 mg/day to 600 mg/day in a slightly greater than proportional manner (Table 3). Letrozole PK parameters (C_{max}, time to maximum plasma concentration, and area under the concentration–time curve) were comparable across all treatment arms (Table 3). The plasma concentration of letrozole increased between four- and five-fold from Day 1 to Day 14.

Pharmacodynamic analyses

Ki67 levels were decreased following study treatment in all 11 evaluable patients with matched baseline and posttreatment tumor samples (Fig. 2). Treatment with single-agent letrozole resulted in a mean decrease in Ki67-expressing cells of 69% (range 38–100%; $n = 2$). The mean percent decrease in Arm 2 (400 mg ribociclib) was 96% (range 78–100%; $n = 6$) and in Arm 3 (600 mg ribociclib) was 92% (range 75–100%; $n = 3$).

Ribociclib PD activity was assessed in tumor samples according to the change in pRb level and any alterations in the expression of cyclin D–CDK4/6–INK4-Rb pathway genes from baseline to Day 15. Baseline levels of pRb varied between patient samples, and both increased and decreased pRb levels from baseline to Day 15 were observed across the three treatment arms. The variation observed between patients in each group, together with the small number of evaluable paired samples ($n = 10$) precludes a definitive conclusion regarding the impact of ribociclib on pRb levels. In Arm 1 (single-agent letrozole), pRb levels increased from baseline to Day 15 in both evaluable patients, while pRb levels decreased in five out of eight evaluable patients in Arms 2 and 3 (Arm 2, $n = 4/6$; Arm 3, $n = 1/2$); the mean percent decrease in pRb levels was 59% (range 31–95%; $n = 5$).

Analysis of cyclin D–CDK4/6–INK4–Rb pathway gene expression in tumor tissue revealed that across 10 evaluable samples, there may be a trend for decreased expression of cyclin D–CDK4/6–INK4–Rb pathway-related genes, such as *CDK4* and *CDK6*, upon ribociclib treatment compared with letrozole treatment alone (Fig. 3). Due to the small number of evaluable patient samples in each group (Arm 1, $n = 2$; Arm 2, $n = 6$; Arm 3, $n = 2$), no conclusions can be made as to any potential dose effect of ribociclib.

The PD activity of letrozole was evaluated according to the change in plasma estradiol levels from baseline to Day 14 in seven evaluable paired tumor samples. Posttreatment estradiol levels were decreased 100% below the LLOQ (0.5 pg/mL) for six of the seven evaluable patients. One patient in Arm 2 had an observed increase in estradiol levels of 243% that was most likely the result of perimenopausal changes (age 51 years).

Table 3
Primary ribociclib and letrozole pharmacokinetic parameters.

Treatment	Analyte	Day	n	C_{max} (ng/mL)[a]	T_{max} (h)[b]	AUC_{0-6h} (ng•h/mL)[a]	AUC_{0-24h} (ng•h/mL)[a]
Arm 1:	Letrozole	1	4	21 (8)	2 (2–4)	76 (23)	–
Letrozole 2.5 mg/day ($n = 4$)		8	4	68 (28)	2 (2–3)	352 (143)[c]	–
		14	3	86 (35)	2 (2–2)	460 (200)	1684 (773)
Arm 2:	Ribociclib	1	5	350 (122)	4 (2–4)	1391 (395)	–
Ribociclib 400 mg/day + letrozole		8	5	906 (419)	4 (2–6)	4338 (2183)	–
2.5 mg/day ($n = 6$)		14	6	1022 (527)	3 (2–6)	4867 (2633)	15,482 (8629)[d]
	Letrozole	1	6	16 (2)	2 (2–5)	62 (8)[d]	–
		8	5	66 (13)	2 (2–6)	335 (61)	–
		14	6	83 (14)	2 (2–6)	450 (78)	1692 (459)[d]
Arm 2:	Ribociclib	1	3	1168 (513)	2 (2–4)	4714 (1607)	–
Ribociclib 600 mg/day + letrozole		8	3	2610 (547)	4 (2–4)	11,173 (1830)	–
2.5 mg/day ($n = 4$)		14	3	3083 (966)	2 (2–2)	13,348 (5461)[e]	38,896 (16,826)[e]
	Letrozole	1	3	19 (7)	2 (2–2)	89 (30)	–
		8	3	65 (14)	2 (2–2)	333 (93)	–
		14	2	88 (9)	2 (2–2)	462 (2)	1577 (90)

Abbreviations: AUC: area under the concentration–time curve; C_{max}: maximum plasma concentration; SD: standard deviation; T_{max}: time to maximum plasma concentration.
[a] Mean (SD).
[b] Median (range).
[c] $n = 3$.
[d] $n = 5$.
[e] $n = 2$.

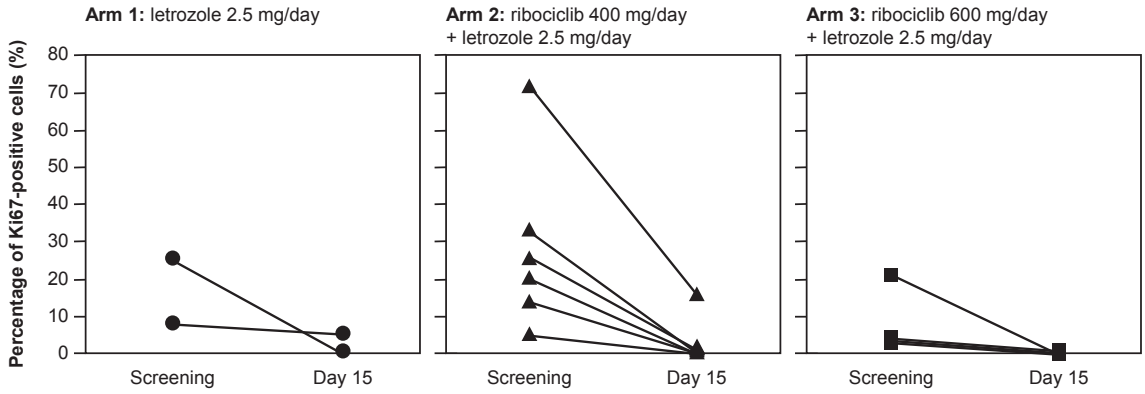


Fig. 2. Posttreatment changes from baseline in the percentage of Ki67-positive cells.

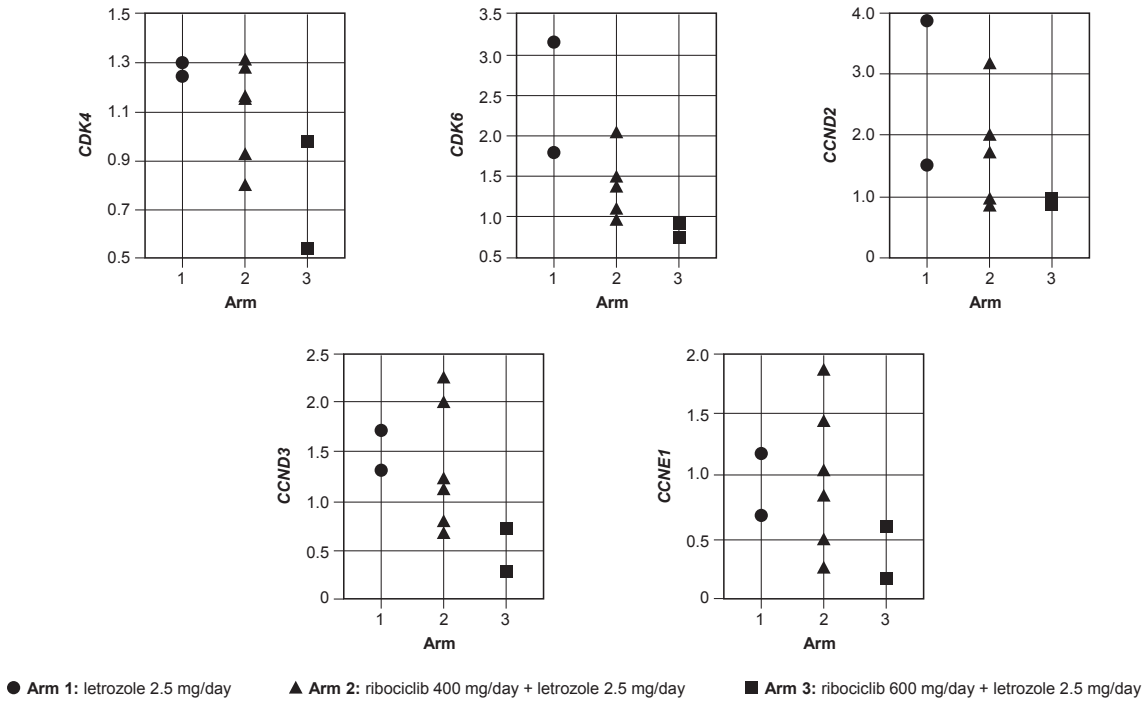


Fig. 3. Expression of genes involved in the cyclin D–CDK4/6–INK4–Rb pathway in each treatment arm presented in strip plots as the fold change from baseline to Day 15. **Abbreviations:** CDK: cyclin-dependent kinase; INK4: inhibitor of CDK4/6; Rb: retinoblastoma.

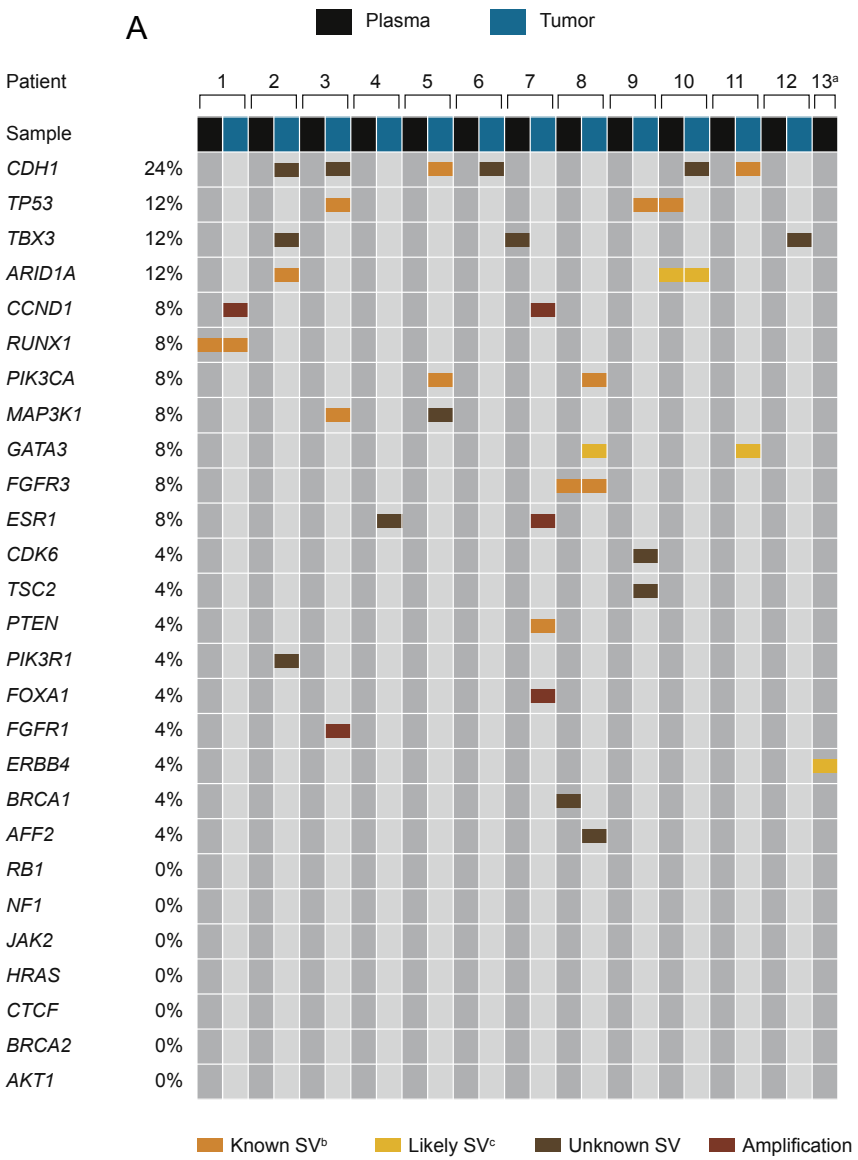
Genetic alterations

NGS analysis was performed on both tumor tissue and plasma ctDNA samples collected from 12 patients, while one patient had only ctDNA samples available for NGS analysis. Tumor sample analysis of over 500 genes identified alterations in commonly reported breast cancer-related genes such as *ARID1A*, *CDH1*, *GATA3*, *PIK3CA*, and *TP53* [10,18] (Fig. 4A). None of the patients had a mutation in the Rb gene (*RB1*). Compared with the results of the tumor sample analysis, alterations were detected in plasma ctDNA samples much less frequently. Plasma ctDNA allelic fractions showed little variation between samples collected at screening and those collected at Day 15 (Fig. 4B).

Discussion

In this window-of-opportunity study, patients with HR+, HER2– early breast cancer received letrozole with or without ribociclib prior to surgery. There were few enrolled patients in each treatment group with evaluable samples, precluding definitive conclusions regarding PK, PD, and biomarker evaluations. Accrual may have been affected by the short duration of therapy, which may have a limited clinical benefit, coupled with the clinical complexity of this window-of-opportunity study (multiple assessments and extensive cardiac monitoring). Other factors that may have affected accrual include ineligibility due to limited tissue availability, HR status, or lesion size. Overall, the combination of ribociclib and letrozole was well tolerated, with no Grade 3/4 AEs reported over a 2-week treatment period. The PK profile of ribociclib in the presence of letrozole was consistent with historical single-agent ribociclib data [19], indicating that ribociclib PK is not substantially affected by letrozole. The direct comparison of letrozole PK parameters across the three treatment arms indicates that there is no significant effect of ribociclib on letrozole PK.

The extent to which letrozole, with or without ribociclib, inhibited cell proliferation was measured according to Ki67 levels.



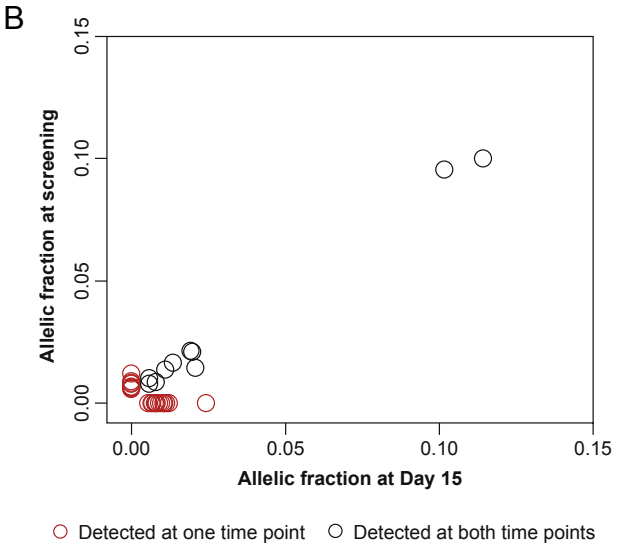


Fig. 4. Genetic alterations in matched tumor tissue and plasma ctDNA samples (A), and allelic fractions in plasma ctDNA at screening and on Day 15 (B). **Abbreviations:** ctDNA: circulating tumor DNA; SV: short variant (single nucleotide variants, insertions, and deletions). [a] Patient 13 did not have an interpretable tumor sample for analysis. [b] Alterations reported ≥2 times in the COSMIC database [36]. [c] Nonsense or frameshift mutations reported <2 times in the COSMIC database [36].

Ki67 decrease in presurgical studies has been demonstrated to be a good predictive marker of the outcome of treatment in larger trials [20], making Ki67 a valuable PD marker of the effectiveness of medical therapy [21]. All patients in this trial experienced a decrease from baseline in the percentage of cells expressing the Ki67 proliferation marker following treatment with either single-agent letrozole or letrozole in combination with ribociclib. These results are in agreement with the known role of ribociclib as a cell cycle inhibitor [12,13] and consistent with the observed reduction in Ki67 levels following treatment with a CDK4/6 inhibitor in combination with anastrozole [22]. Recent clinical trial data demonstrate the clinical benefit of ribociclib in combination with endocrine therapy, including exemestane [23] and letrozole [16], in patients with ER+, HER2− breast cancer. Additionally, co-administration of a CDK4/6 inhibitor with either letrozole [24] or fulvestrant [25] significantly prolonged the progression-free survival of postmenopausal women with HR+, HER2− advanced breast cancer.

Signs of cyclin D–CDK4/6–INK4–Rb pathway inhibition were also observed with ribociclib treatment. Decreased pRb levels were observed in five out of eight evaluable patients treated with ribociclib. The lack of a decrease in pRb levels following ribociclib treatment in some patient samples could be explained by potential activity of ribociclib on phosphorylation sites other than S780, which were not assessed in this study. Rb contains 13 sites for CDK phosphorylation [26], yet the number and combination of sites required for cell cycle control remains unknown [27]; thus a lack of S780 dephosphorylation may not directly correlate with Rb activity. Additionally, although IHC is a critical component of tumor characterization, there is a degree of inherent subjectivity and variability [28]. The small sample size in this study, combined with variability and inherent issues of IHC quantitation, means the results cannot be clearly interpreted. On-target inhibition of the cyclin D–CDK4/6–INK4-Rb pathway was also suggested by the analysis of cyclin D–CDK4/6–INK4–Rb pathway gene expression.

Recent studies have suggested the potential of using ctDNA analysis as a less invasive method of tumor molecular characterization [29] and to inform prognosis in early-stage and metastatic breast cancer [30]. Studies have demonstrated the ability of ctDNA profiling to detect mutations in target genes [31,32]. However, in line with other reports [29,33] this study highlights the potential challenges in utilizing ctDNA in the context of newly diagnosed breast cancer with low levels of tumor DNA in the circulation. Detection levels of ctDNA are >50% in the case of non-metastatic breast cancer compared with >75% in metastatic breast cancer [29] and have been reported as low as 24% in some cases [33]. Technical advancements that improve the sensitivity and specificity of ctDNA analysis should enable ctDNA analysis to detect and characterize early disease states [34]. In this study, few genetic alterations were detected in ctDNA samples in comparison with tumor samples. Analysis of ctDNA samples showed robustness across time points, with concordance in allelic fractions between baseline and Day 15. However, further studies of concordance are needed in patients with higher levels of tumor DNA in the circulation.

Conclusions

Collectively, the findings from this study indicated that the combination of ribociclib and letrozole was associated with an acceptable safety profile over a 2-week treatment period. The comparison of letrozole PK parameters across all treatment arms suggests the absence of a drug–drug interaction between ribociclib and letrozole. The ability of ribociclib in combination with letrozole to improve progression-free survival compared with letrozole single-agent has recently been confirmed in the Phase III MONALEESA-2 trial [35] in postmenopausal patients with HR+, HER2− advanced breast cancer (ClinicalTrials.gov study number: NCT01958021).

Ethical approvals

The study protocol and amendments were reviewed by the Independent Ethics Committee/Institutional Review Board for each center. The study was conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all study participants.

Conflict of interest statement

This study was initiated, funded, and sponsored by Novartis Pharmaceuticals Corporation, who also provided financial support for medical editorial assistance. S. Dhuria, Z. Tang, N. Solovieff, M. Miller, and E. Di Tomaso are Novartis employees; Z. Tang holds Novartis stock and options. F. Meric-Bernstam served as a consultant to, and received research funding from, Novartis. Outside the submitted work, F. Meric-Bernstam served as a consultant to Celgene, Genentech, Inflection Biosciences, and Roche, received research funding from Aileron Therapeutics, AstraZeneca, Bayer, Calithera, CytomX Therapeutics, Debiopharm, Puma Biotechnology, Taiho, and Veastem, and honoraria from Genentech and Roche. M.P. Lolkema received research funding from Astellas Pharma and Johnson & Johnson outside the submitted work. A. Bardia acted as a consultant for Novartis outside the submitted work. S.A. Hurvitz received related research funding from Novartis and institute research funding from Bayer, Lilly, and OBI Pharma outside the submitted work. G. Curigliano, P. Gómez Pardo, P. Conte, J.T. Beck, and F. Penault-Llorca declare no conflicts of interest.

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